



# IMPROVING THE LIVES OF PEOPLE WITH NEURODEVELOPMENTAL DISABILITIES

1 March 2023

# Forward looking statements

This presentation contains forward looking statements that involve risks and uncertainties. Although we believe that the expectations reflected in the forward looking statements are reasonable at this time, Neuren can give no assurance that these expectations will prove to be correct. Actual results could differ materially from those anticipated. Reasons may include risks associated with drug development and manufacture, risks inherent in the regulatory processes, delays in clinical trials, risks associated with patent protection, future capital needs or other general risks or factors.

# Global leader in neurodevelopmental disorder therapy development

Developing new therapies for debilitating neurodevelopmental disorders that emerge in early childhood and are characterised by impaired connections and signalling between brain cells

**2** novel drugs, treating **6** neurodevelopmental disorders, all with **Orphan Drug** designation, with no existing approved therapies<sup>1</sup>

Neuren **owns all intellectual property**, with no royalties payable to 3<sup>rd</sup> parties

Incorporated in New Zealand, based in Melbourne, Australia, listed on ASX (Code: NEU)

<sup>1</sup> Except growth hormone to treat some aspects of Prader-Willi syndrome

1

NDA for trofinetide to treat Rett syndrome under Priority Review by FDA with PDUFA action date of 12 March 2023

2

Potential revenue from Acadia in 2023 for Rett syndrome in the US alone of US\$73m (A\$104 million)<sup>1</sup> plus double-digit % royalties

3

Strong partnering interest received for trofinetide outside North America

4

Accelerating Phase 2 development of NNZ-2591 in 4 indications, with potential markets 5x Rett syndrome

5

NNZ-2591 novel mechanism of action has many more potential applications

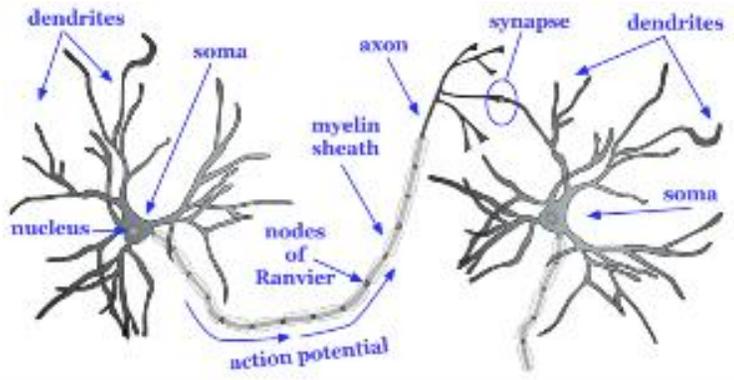
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A\$40 million cash at 31 December 2022 – well funded to execute NNZ-2591 Phase 2 trials and preparation for Phase 3

<sup>1</sup> Assuming a New Drug Application (NDA) is approved by the FDA, the product is launched in the US, US\$33m is received as one third share of the value of a Rare Pediatric Disease Priority Review Voucher if awarded upon approval of a NDA, and a USD/AUD exchange rate of 0.70

# Seeking a ground-breaking impact on neurodevelopmental disorders

Rett	Fragile X	Phelan-McDermid	Angelman	Pitt Hopkins	Prader-Willi
<i>MECP2</i>	<i>FMR1</i>	<i>SHANK3</i>	<i>UBE3A</i>	<i>TCF4</i>	<i>15q11-q13</i>



Impaired communication between neurons, abnormal formation/pruning of dendrites & chronic inflammation

Neuren's drugs target the critical role of IGF-1 in this upstream process, using analogs of peptides that can be taken orally as liquids

## Severe impact on nearly every aspect of life

walking and balance issues  
speech impairment  
impaired hand use

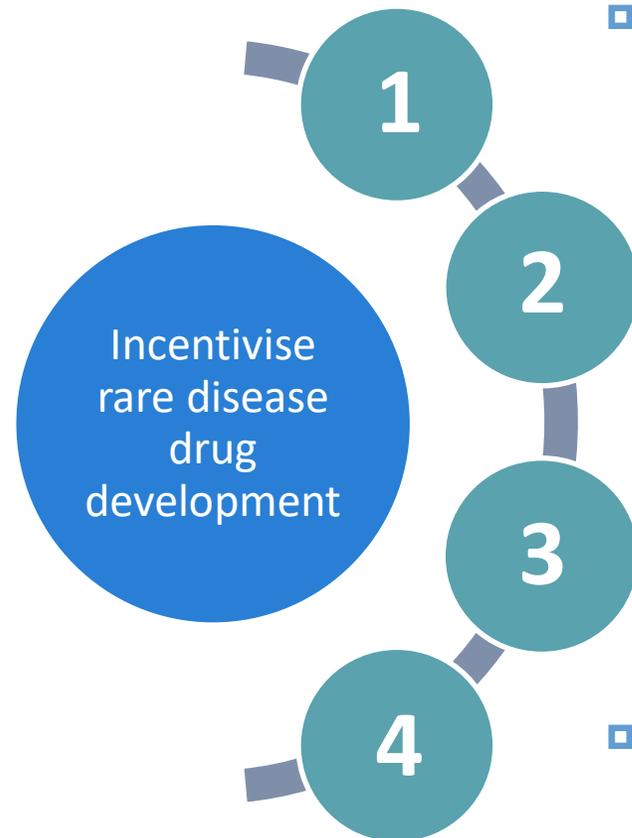
anxiety and hyperactivity  
intellectual disability  
sleep disturbance

seizures  
breathing irregularities  
gastrointestinal problems

# All programs at Phase 2 or later and Orphan Drug designation

Compound	Indication	Preclinical	Phase 1	Phase 2	Phase 3	Registration	Commercial rights	
Trofinetide	Rett NA	[Progress bar]					<i>PDUFA date 12 Mar 2023</i>	ACADIA
	Rett RoW	[Progress bar]						neuren
	Fragile X	[Progress bar]						NA: ACADIA RoW: neuren
NNZ-2591	Phelan-McDermid	[Progress bar]						neuren
	Angelman	[Progress bar]						
	Pitt Hopkins	[Progress bar]						
	Prader-Willi	[Progress bar]						

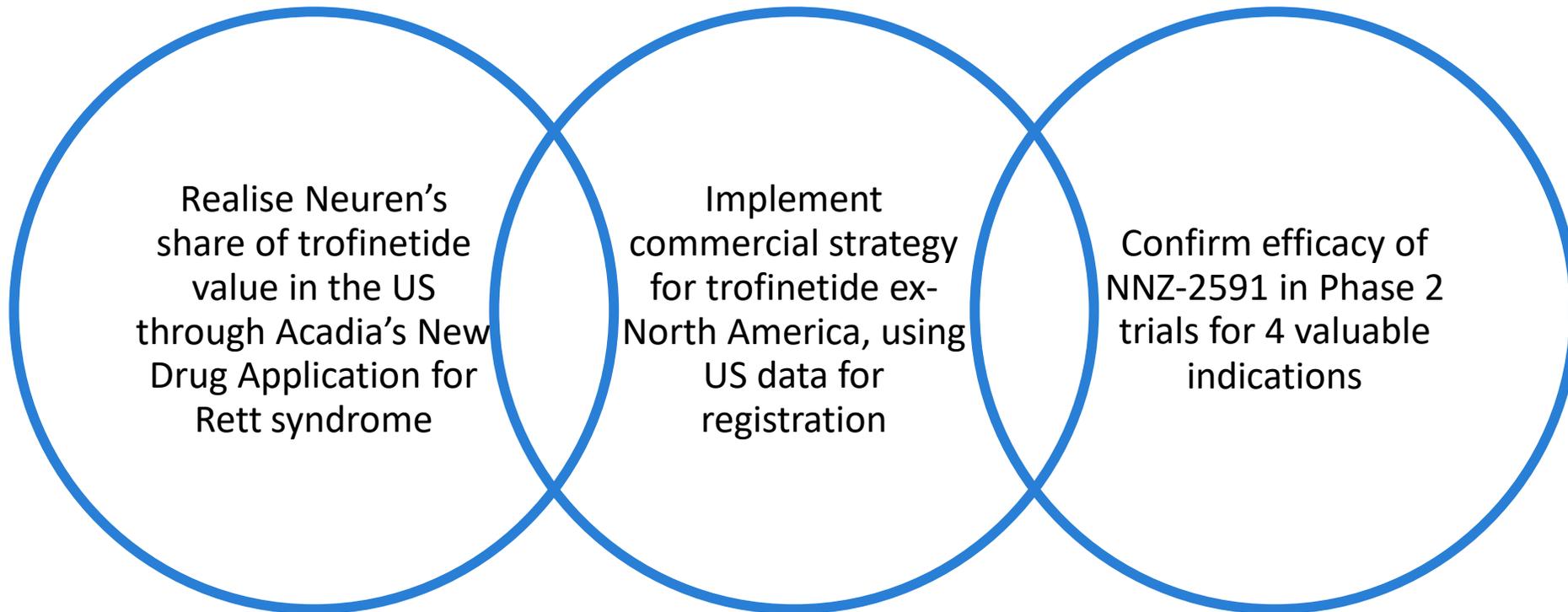
Neuren is targeting multiple “rare diseases”, but they are not “ultra-rare”



- Marketing exclusivity periods protect against generics independent of patents (7.5 years in US, 12 years in EU, 10 years in Japan, South Korea and Taiwan, China has proposed to introduce 7 years)
- Priority review by regulators (e.g. 6 months in US instead of 10 months) and higher probability of approval
- Urgent unmet need results in strong engagement from patient community and leading physicians, and immediate access to known patients
- Attractive pricing environment (average US Orphan Drug price of US\$186,758 per patient p.a. in 2017<sup>1</sup>)

<sup>1</sup> AHIP

# Three key drivers transforming near term value

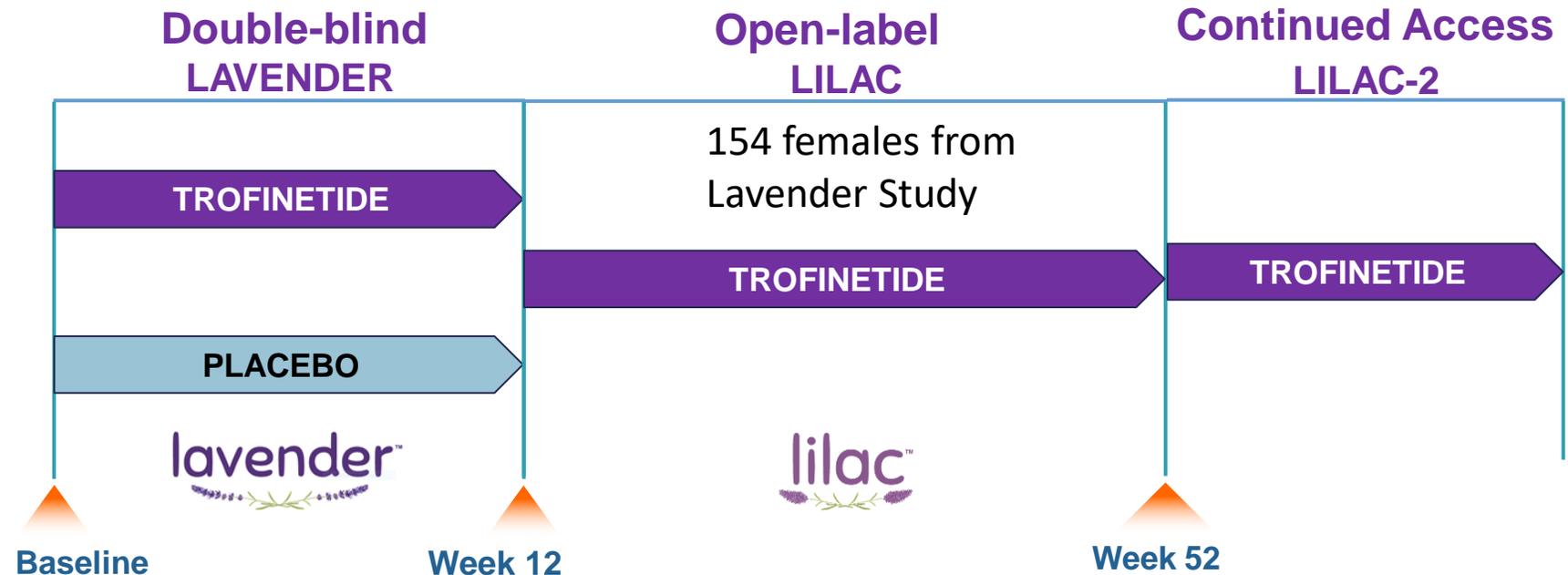


# Rett syndrome Phase 3 and NDA

- Acadia submitted NDA in July 2022 for treatment of Rett syndrome in patients two years of age and older
- NDA based on pivotal efficacy from positive Phase 3 trial, supportive efficacy from Neuren's positive Phase 2 trial, safety data from completed and ongoing studies
- FDA accepted NDA for Priority Review - PDUFA action date set for 12 March 2023
- FDA advised that at this time it is not planning to hold an Advisory Committee meeting

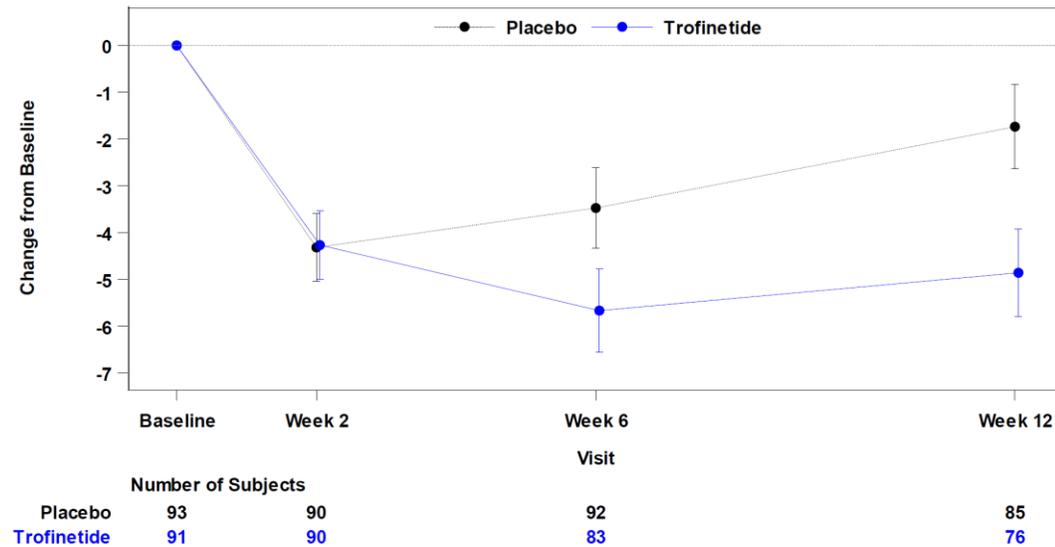
LAVENDER™ randomised, double-blind, placebo-controlled trial:

- 187 females aged 5 to 20 years
- RSBQ (caregiver) and CGI-I (physician) at 12 weeks co-primary efficacy endpoints



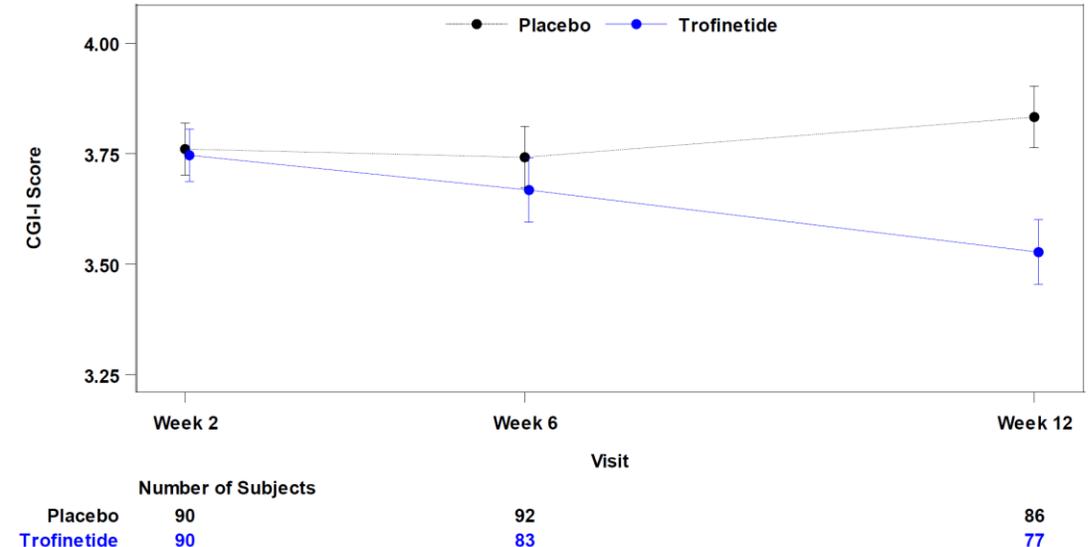
# Positive Phase 3 results

## Rett Syndrome Behavioural Questionnaire (RSBQ)



Change from Baseline	Placebo	Trofinetide*
Mean	-1.7	-5.1
<i>p-value</i>		0.0175
<i>Effect Size</i>		0.37

## Clinical Global Impression – Improvement (CGI-I)

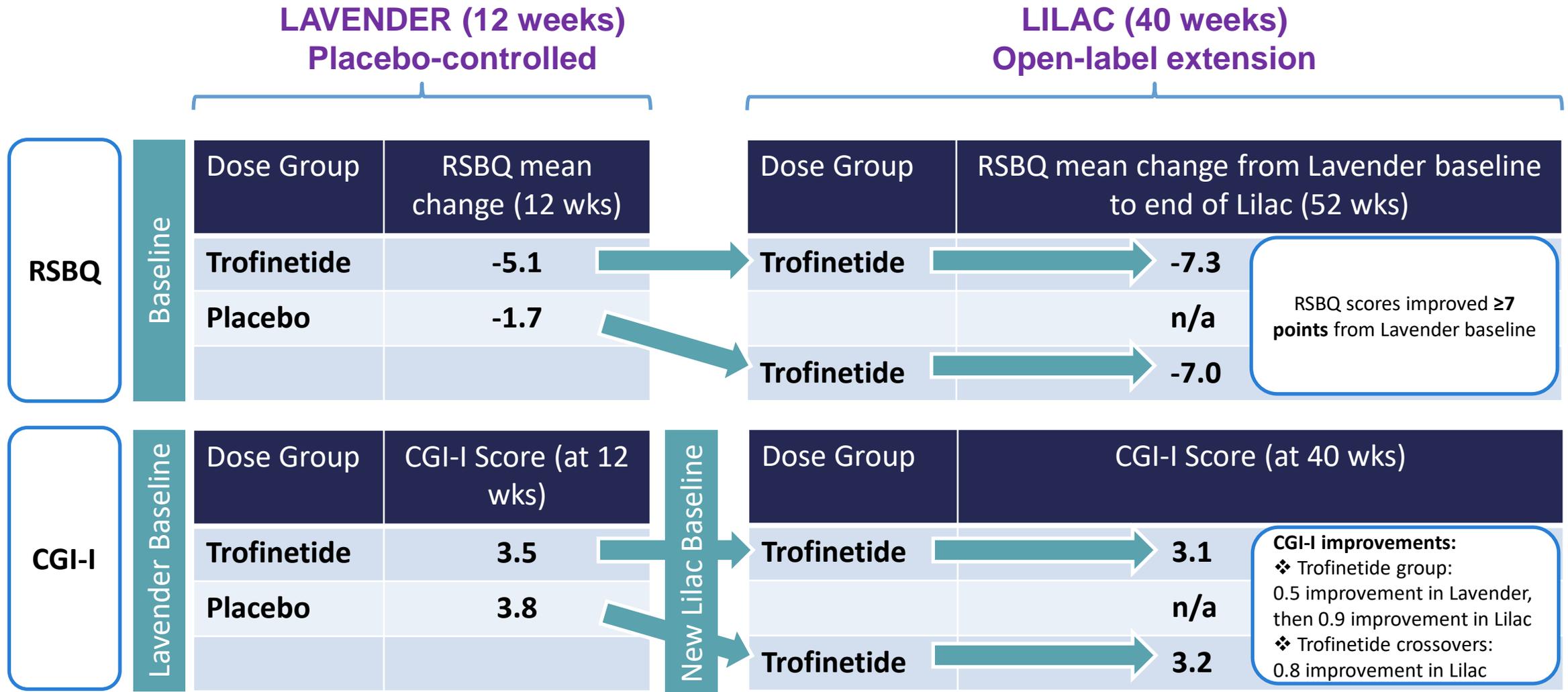


Week 12 Score	Placebo	Trofinetide*
CGI-I	3.8	3.5
<i>p-value</i>		0.0030
<i>Effect Size</i>		0.47

Source: Acadia presentation ([Acadia Corporate Presentation \(4Q22 Earnings\)](#), [Lavender Study Results \(acadia.com\)](#))

\* RSBQ mean (SE) baseline score placebo = 44.5 (1.26) and trofinetide = 43.7 (1.21). CGI-I no baseline score. CGI-I uses a 7-point Likert scale; with a score of 4 = no improvement; >4 = worsening and <4 = improvement. *p*-values based on least squares mean from the mixed-effects model for repeated measures analysis.

# Sustained and continued improvement observed in Lilac



Source: Acadia presentation ([Acadia Corporate Presentation \(4Q22 Earnings\)](#), [Lavender Study Results \(acadia.com\)](#))

RSBQ: n=161 for Lavender at 12 weeks; n=88 for Lilac at 40 weeks.

CGI-I: n=163 for Lavender at 12 weeks; n=91 for Lilac at 40 weeks. CGI-I uses a 7-point Likert scale; a score of 4 = no improvement; >4 = worsening and <4 = improvement.

# Consistent safety and tolerability findings

## LAVENDER (12 weeks) Placebo-controlled

	Adverse Events (AEs) >10% observed in Trofinetide group
Diarrhea	80.7% (97% Mild and Moderate)
Vomiting	27.0% (96% Mild and Moderate)

## LILAC (40 weeks) Open-label extension

	Adverse Events (AEs) >10% observed in Lilac
Diarrhea	74.7% (96% Mild and Moderate)
Vomiting	28.6% (100% Mild and Moderate)
COVID-19	11%
<i>Discontinuations due to AE of diarrhea: 21%</i>	

No new safety or tolerability findings in Lilac



# 5x larger opportunity for NNZ-2591

Disorder	Gene mutation	Published prevalence estimates	Potential patients		
			US <sup>1</sup>	Europe <sup>1</sup>	Asia <sup>1, 2</sup>
Phelan-McDermid	<i>SHANK3</i>	1/8,000 to 1/15,000 males and females	22,000	28,000	81,000
Angelman	<i>UBE3A</i>	1/12,000 to 1/24,000 males and females	14,000	18,000	52,000
Pitt Hopkins	<i>TCF4</i>	1/34,000 to 1/41,000 males and females	7,000	9,000	25,000
Prader-Willi	<i>15q11-q13</i>	1/10,000 to 1/30,000 males and females	13,000	16,000	47,000
			<b>56,000</b>	<b>71,000</b>	<b>205,000</b>

- Current opportunity for NNZ-2591 is more than 5 times the Rett Syndrome opportunity<sup>3</sup>
- There are many other neurodevelopmental disorders potentially relevant for NNZ-2591 mechanism of action
- Neuren retains global rights

<sup>1</sup> Estimates derived by applying the mid-point of the prevalence estimate range to the populations under 60 years

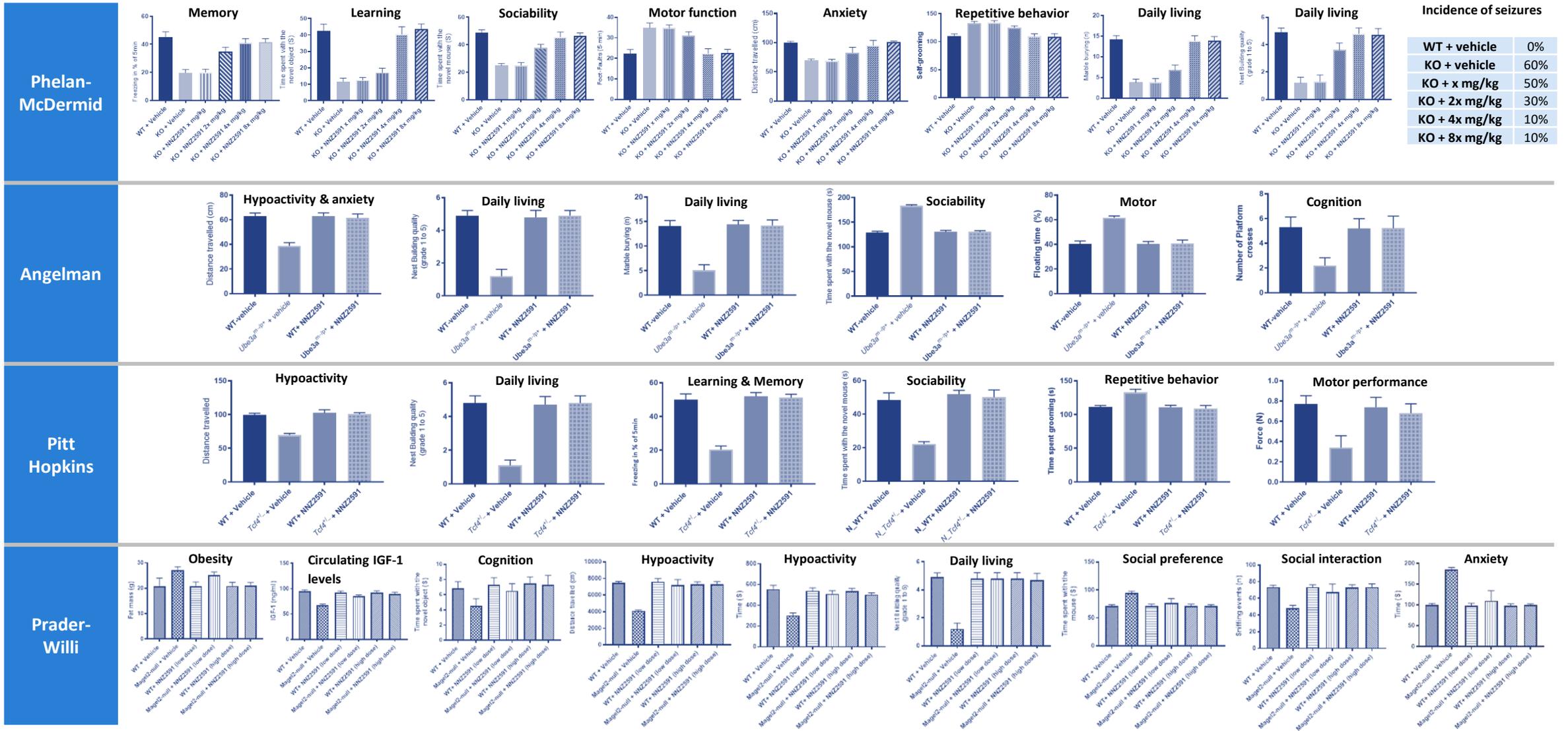
<sup>2</sup> Asia comprises Japan, Korea, Taiwan, Israel and urban populations of China and Russia

<sup>3</sup> Based on number of potential patients globally

# NNZ-2591 has ideal attributes leading into Phase 2

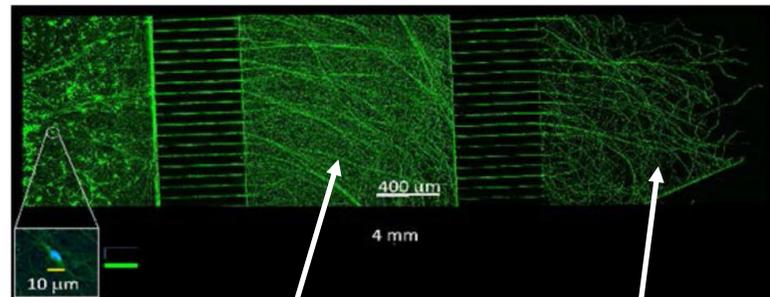
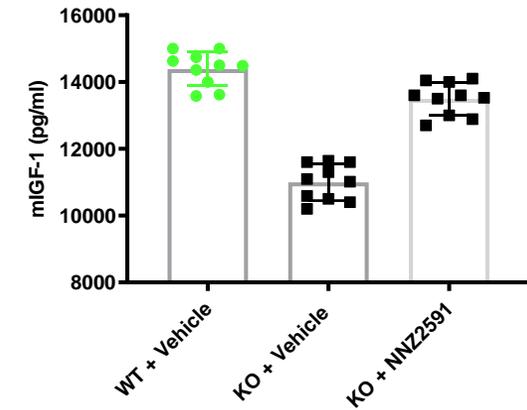
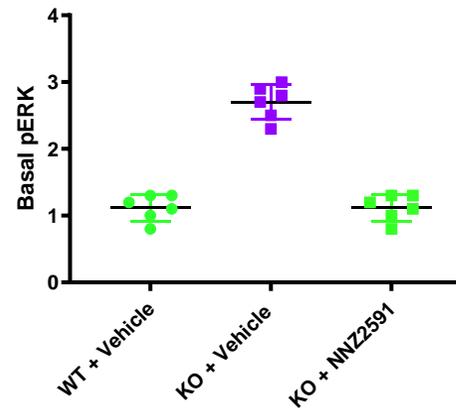
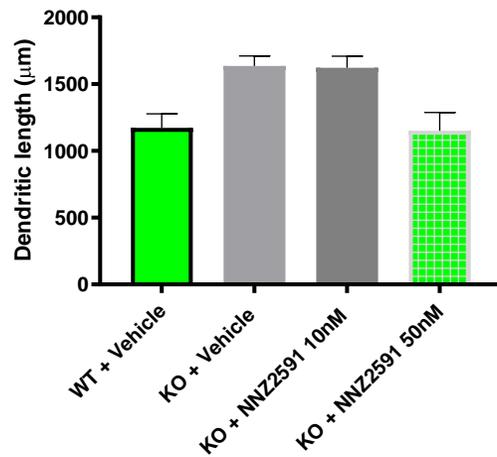
- ✓ Novel mechanism of action
- ✓ Clear and consistent efficacy in mouse models of each syndrome
- ✓ Biochemical effects in the brain confirmed
- ✓ Optimum dose identified
- ✓ Demonstrated high oral bioavailability and blood-brain barrier penetration
- ✓ IND-enabling program of non-clinical toxicology and CMC studies completed
- ✓ Proprietary drug substance manufacturing process with exceptional purity and high yield, administered as patient-friendly liquid dose
- ✓ Safe and well tolerated in Phase 1 trial
- ✓ Orphan designations from FDA and EMA
- ✓ INDs approved by FDA for Phelan-McDermid, Angelman, Pitt Hopkins and Prader-Willi syndromes

# Clear and consistent efficacy in animal models



# Biochemical effects confirmed

In biochemical testing, NNZ-2591 was shown to normalise the abnormal length of dendrite spines between brain cells, the excess activated ERK protein (pERK) and the depressed level of IGF-1 in *shank3* knockout mice



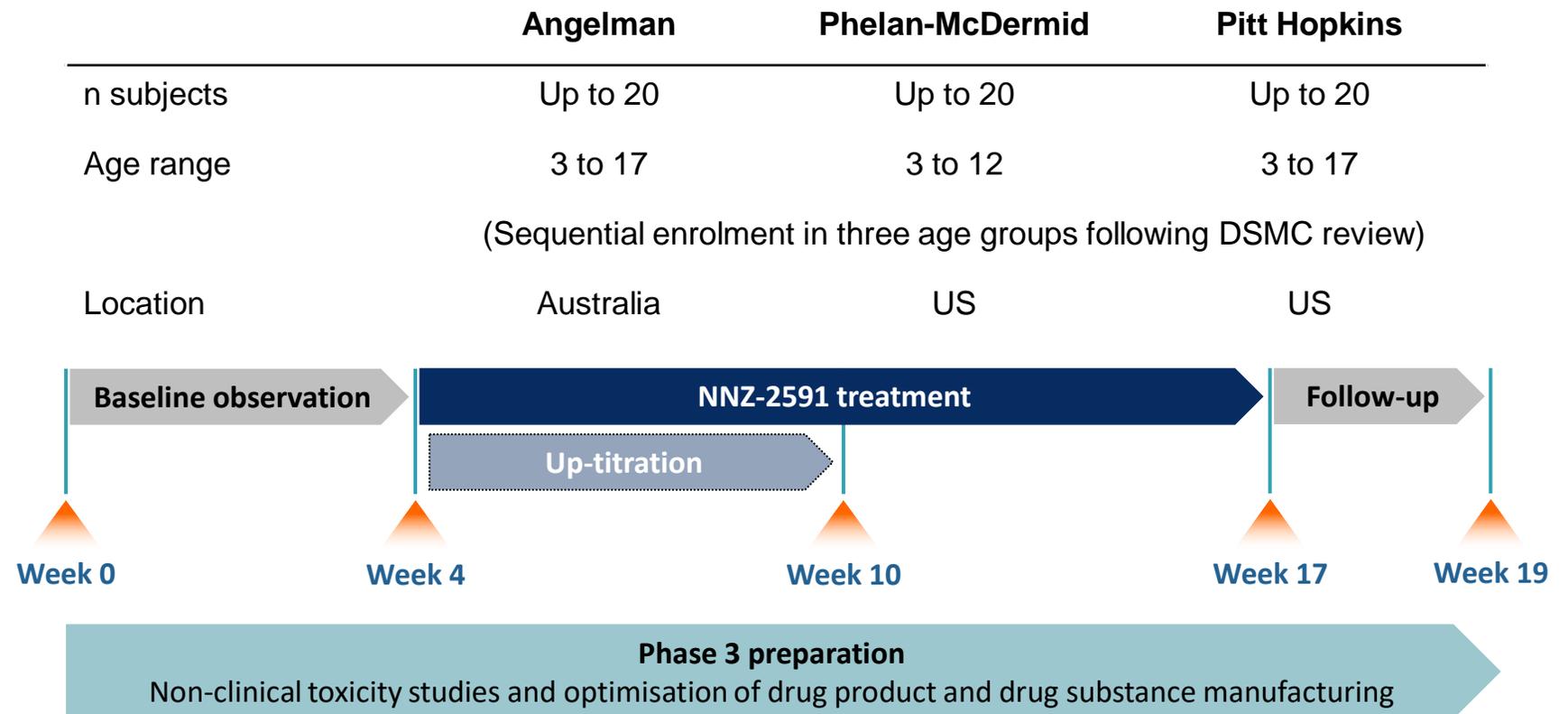
Abnormal dendrites in *shank3* knockout mice

Normalisation after treatment with NNZ-2591

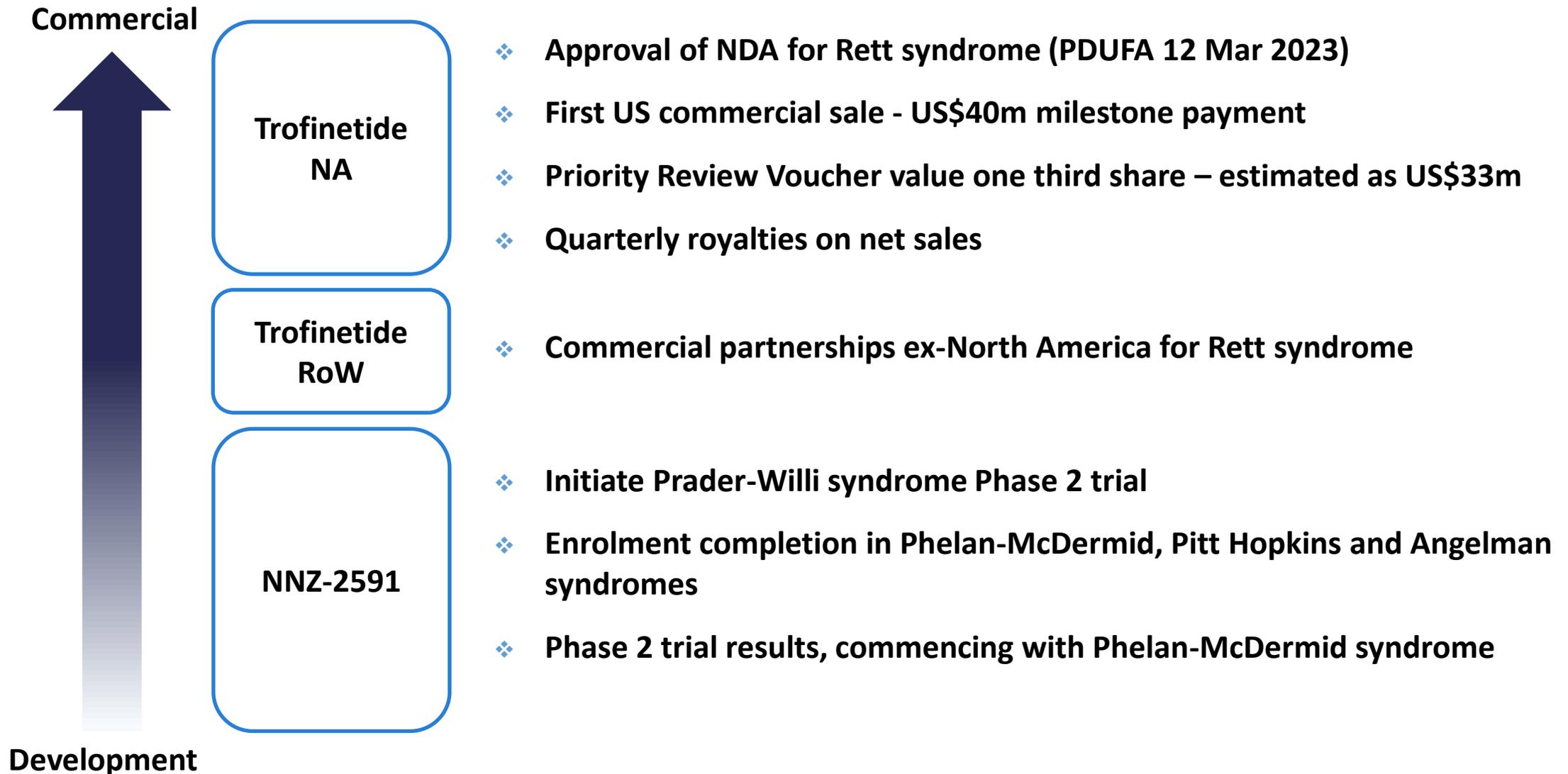
# Key features of first Phase 2 trials

**Overall aim – expedite data that enables subsequent trials to be designed as registration trials and prepare for Phase 3 in parallel**

- Prioritising speed to data
- Maximising opportunity to demonstrate effects
- Confirm safety and PK in pediatric patients
- Assess treatment impact across multiple efficacy measures to select primary endpoint for registration trial
- Series of Phase 2 trial results, commencing with Phelan-McDermid syndrome in H2 2023



# Transforming catalysts in 2023



# CONTACT

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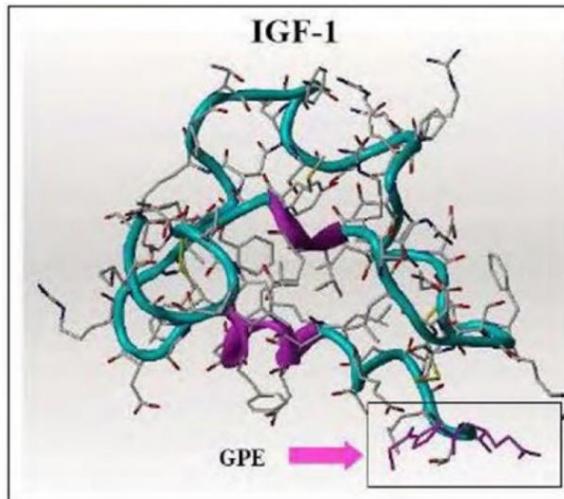
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## Trofinetide

- ❑ Trofinetide is an investigational drug and a novel synthetic analog of GPE, the amino-terminal tripeptide of IGF-1



GPE=glycine-proline-glutamate; IGF-1= Insulin-like growth factor 1

## Proposed Mechanism of Action<sup>1</sup>

### Rett syndrome features:

- ❑ Insufficient formation of new synapses by neurons
- ❑ Excessive pruning of existing synapses by overactive microglia

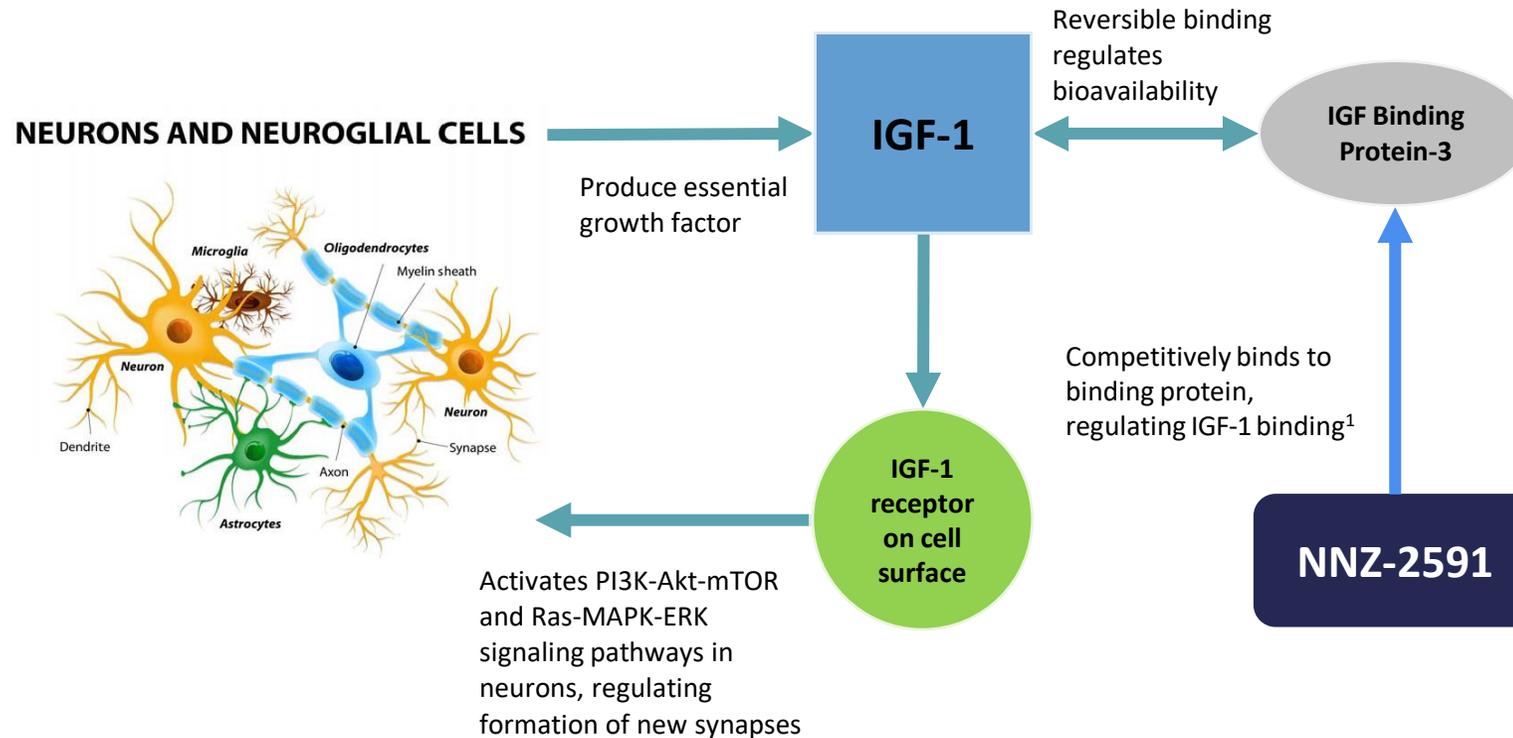
### Trofinetide is thought to:

- ❑ Improve synaptic function and restore synaptic structure
- ❑ Inhibit overactivation of inflammatory microglia and astrocytes
- ❑ Increase the amount of IGF-1 in the brain

<sup>1</sup> Chahrour, Science, 2008; Itoh, J Neuropath Exp Neurol, 2007; Bourguignon, Brain Res, 1999; Tropea, PNAS, 2009

Source: Acadia Lavender Study Results Presentation <https://ir.acadia-pharm.com/static-files/84457c64-60ab-4b2f-a166-edc1d465f4a8>

# Novel mechanisms of action – NNZ-2591



- **NNZ-2591** is a synthetic analog of cyclic glycine proline, a peptide that occurs naturally in the brain, designed to be more stable, orally bioavailable and readily cross the blood-brain barrier
- **NNZ-2591** can regulate the amount of IGF-1 that is available to activate IGF-1 receptors
- The effects of **NNZ-2591** are “state-dependent” – correcting impairment, but not impacting normal cells

<sup>1</sup> doi: 10.1038/srep04388: Guan et al, 2017: Cyclic glycine-proline (cGP) regulates IGF-1 homeostasis by altering the binding of IGFBP-3 to IGF-1